Medical Science

25(109), March, 2021

Statins induced transaminitis in Iraqi patients with dyslipidemia

Thuraya Salim Abed[1], **Gheyath Al Gawwam**[2], **Hayder A Fawzi**[3]✉

To Cite:
Abed TS, Al Gawwam G, Fawzi HA. Statins induced transaminitis in Iraqi patients with dyslipidemia. *Medical Science*, 2021, 25(109), 739-743

Author Affiliation:
[1]Baghdad Medical city, Ministry of health, Baghdad, Iraq
[2]College of Medicine, Baghdad University, Baghdad, Iraq
[3]Department of pharmacy, Al Rasheed University College, Baghdad, Iraq

✉**Corresponding author**
Department of pharmacy, Al Rasheed University College, Baghdad,
Iraq;
Email: hayder.adnan2010@gmail.com

Peer-Review History
Received: 20 February 2021
Reviewed & Revised: 22/February/2021 to 18/March/2021
Accepted: 19 March 2021
Published: March 2021

Peer-review Method
External peer-review was done through double-blind method.

ABSTRACT

Objective: assess the effect of using statins on liver enzymes in patients with dyslipidemia. *Methods*: A prospective observational study, the study involved 140 participants that were initiated on statin therapy at the end of the study 104 patients completed the study. Age of the patients ranged from 35 – 74 years. All patients examined after 6 months to assess the elevation in aminotransferase and bilirubin levels. *Results*: After 3 and 6 months; there was a significant elevation of serum AST, ALT, and bilirubin. However only 2.9% and 3.8% of the patients had an elevation (more than 2 upper normal limit) in serum AST and ALT respectively. The most common side effect was muscle ache. *Conclusions*: statins is appear to safe drug, despit there an elevation in some of liver enzymes in this study this elevation is mostely biochemical in natural. In term other side effect statins showed good telerobilty with muscle ache being the most common side effect.

Keywords: statins, liver enzymes, safety, prospective, cohort

1. INTRODUCTION

Statins are a potent with good safety profile for the management of elevated blood lipids. These drugs are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes an early, rate-limiting step in cholesterol biosynthesis (Endo, 2010). After oral administration, intestinal absorption of the statins varies between 30% and 85%. All of the statins, except simvastatin and lovastatin, are administered as active β-hydroxy acids. Simvastatin and lovastatin are administered as inactive lactones that must be transformed in the liver to their respective β – hydroxy acids (Garcia et al., 2003).

Statins show high safety profile compared to most of the other types of medication for treating dyslipidemia, there low rate of hepatic impairment, however it remains an important adverse event due to its serious consequences. Myopathy remains an important side effect (Rosenson, 2004). Most of the studies revealed about 3% rate of continuous elevation of liver enzymes after using statins which happened the first 3 months of starting the medication. Rare episodes of more severe liver injury have also been seen, and one study suggested that these predominantly occur three to four months after initiation of statin therapy (Newman et al., 2003).

2. PATIENTS AND METHODS

A prospective observational study consists of 140 subjects (36 patients was withdrawn because they did not report to the hospital after 3 and/or 6 months), with age range of 35 – 74 years. The study conducted in the medical city teaching complex, Baghdad from February to November 2019. The patients group consists of 140 subjects who are diagnosed as hyperlipidemia, who are starting statin therapy only as measure for decrease lipid profile and compliance with it or not. Subjects with diagnosed Diabetes mellitus, Heart failure, chronic kidney disease, and thyroid disease were excluded from the study.

All recruits interviewed in outpatient clinic in Baghdad teaching hospital written consent was giving by each subject before participation in this study. Body weight, height and body mass index are measured. Serum lipid panel were measured by using Cobas module C3 11, this is done in (Medical city, Baghdad). Serum sample were taking for lipid panel and liver enzyme done by same laboratory of Baghdad Teaching Hospital.

Statistical Analysis

Data of the study groups were entered in computerized data base software (Microsoft excel software 2010), all variables were coded and transferred into statistical analysis computerized package; MINITAB ® 16.1.1 (2010) and used for data management and analysis.

Chi square was used to assess the significance of differences in between patients and controls in categorical variables. Student's independent (t) test was used to assess the significance of differences in between study groups in continuous variables. Level of significance (α value = 0.05) with $p \leq 0.05$ considered significant. Also one factorial two way ANOVA analyses was used to assess the statistical significance when comparing lipid profile and liver induces among different duration.

3. RESULTS

The study included 140 patients with the majority aged between 45 – 54 years (36.5%), 67.3% were females, as illustrated in table 1. Serum AST, ALT and bilirubin significantly increased after 3 and 6 months from the start of the study, as illustrated in table 2. Only 2.9% of patients had more 2 times upper normal limits (UNL) for AST, and 3.8% increase in 2 times UNL increase in ALT, as illustrated in table 3 and figure 1.

Table 1 Socio-demographic characteristics of the patients

Factor	Description	Number of patients	Percentage	P value
Age	35 - 44	18	17.3076	<0.001
	45 - 54	38	36.53846	
	55 - 64	34	32.69231	
	65 - 74	14	13.46154	
Gander	Female	70	67.30769	<0.001
	male	34	32.69231	
BMI	18.5 - 25	7	6.73	<0.001
	25.1 - 30	30	28.85	
	30.1 - 40	41	39.42	
	> 40.1	26	25.00	

Table 2 Comparison between AST, ALT, and bilirubin levels at different duration

Factor	Baseline		3 months		6 months		P value
	Mean	St Dev	Mean	St Dev	Mean	St Dev	
AST (IU/ml)	18.184	8.011	24.155	9.833	29.243	11.079	<0.0001
ALT (IU/ml	18.01	8.88	25.23	10.34	31.25	12.91	<0.0001
Total bilirubin (mg/dL)	0.5138	0.4908	0.8615	0.6866	1.1369	0.7480	<0.0001

Table 3 distribution of AST and ALT serum level after classified into 4 groups.

	No of patients	Percent
Serum AST		
> 60 IU	3	2.9
40 - 60	10	9.6
20 - 39	81	77.9
normal	10	9.6
Serum ALT		
> 60 IU	4	3.8
40 - 60	16	15.4
20 - 39	70	67.3
normal	13	12.5
Only one patient fit Hy's classification of severe statin liver induced injury with total bilirubin 2X and >3X AST levels and was in rosuvastatin group (1%)		

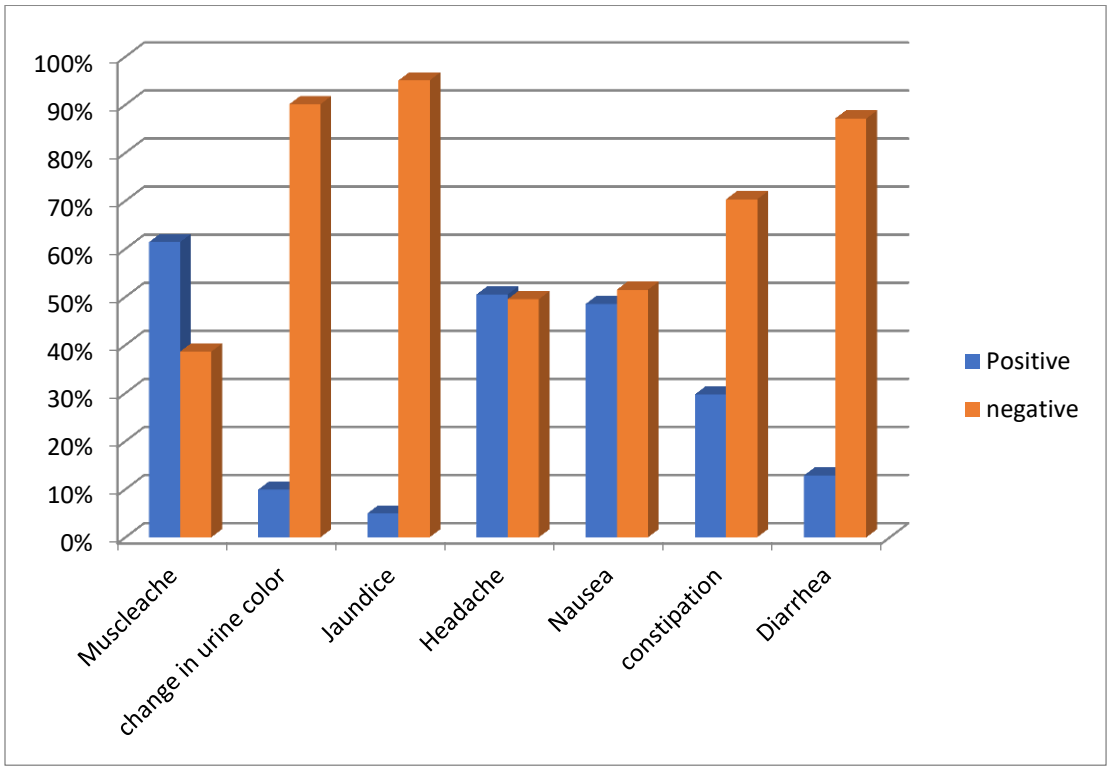

Figure 1 Percentage of patient reported side effect

4. DISCUSSION

In this study statins were well tolerated that the patients did not discontinue treatment because of side effect. The most common side effect reported was muscle ache, headache, nausea, constipation, and diarrhea; these in term of patients reported side effect which more pronounce compared to the side effect reported with official drug label reported to the FDA, this in part may be due to the fact that most of the patient are obese with co morbid condition that have already disease and the possible effect of poly pharmacy as drug interaction may increase these side effect. There was an asymptomatic elevation in liver aminotransferase enzyme, with only 3% AST, and 4% ALT with an >3X UNL of them which is consider as clinical hepatitis (The definition of acute, not infectious or alcoholic, hepatitis in this study was based on an American College of Cardiology guideline stated as "a clinical diagnosis of hepatitis requiring hospitalization, with levels of serum ALT elevated to > three times the ULN") (38,7); however only 1% of patients met Hy's criteria for severe liver injury, with no evidence of liver dysfunction (definition of serious drug induced

liver injury is the development of jaundice (total bilirubin >2Xupper limit of normal) after aminotransferase elevations, which is referred to as Hy's law after observations made by the hepatologist Hy Zimmerman. So overall regarding this point the statins as whole in this study was safe in consent with all previous studies.

In all statin groups (except for atorvastatin) there was dose related increase in liver enzymes, which is similar to other studies that show this dose related effect of statin on liver enzyme. Despite this increase it was not statistically significant (except in rosuvastatin and Fluvastatin groups), it possibly because hyperlipidemic patients may have spontaneous fluctuations in transaminases whether or not they receive statins (Bersano et al., 2008). However, the natural history of elevated aminotransferases if the statins are continued at the same doses is not well known (Bersano et al., 2008) and is not followed in this study for longer than 6 months. There is a suggestion that such patients may exhibit "adaptation" and their aminotransferases remains table or trend downwards even when statins are continued (Bersano et al., 2008).

Statins (except for rosuvastatin) show similar pattern of increment in aminotransferase (parallel) which trend upward showing similarity in their transaminase activity on the liver; but of concern the sharp increase in aminotransferase caused by rosuvastatin in contrary to body of evidence supplied by literatures of minimum effect on the liver enzyme activities (the only patient who met Hy's criteria of drug induced liver injury was in rosuvastatin group however which did not show clinical evidence of liver injury). There is no evidence to suggest that patients who receive higher doses of statins are more likely to develop clinically significant liver injury. Similarly, there exists no convincing relationship between older age, gender, underlying co morbidities (including liver disease) or type of statin and the risk of significant liver injury from statins (Bersano et al., 2008).

It has been speculated that increased aminotransferases may actually represent a pharmacodynamic effect of lipid lowering, rather than a direct effect of the statins. This explanation appears to be a plausible because asymptomatic elevation in aminotransferases occurs with all lipid-lowering agents including ezetimibe which has no effect on hepatic cholesterol synthesis or bile acid excretion (Ward et al., 2019). Concerning simvastatin group the patients had elevated baseline transaminase (mean AST 24.38, and ALT 25.15), despite this elevated baseline transaminase after six months the elevation in transaminase is not statistically significant and less than 2X elevation indicating that it was not clinically significant (only biochemical elevation, insignificant statistically).

It had shown that hyperlipidemic patients with elevated baseline liver enzymes are at not higher risk for hepatotoxicity (as defined biochemically) than hyperlipidemic patients with normal transaminases. The incidence of statin hepatotoxicity over a 6-month period in 342 hyperlipidemic patients with elevated baseline enzymes (AST >40 IU/L or ALT >35 IU/L) who received statins was compared to 1437 hyperlipidemic patients with normal aminotransferases who received statins (statin controls) and 2245 patients with elevated liver enzymes who did not receive statins (liver disease controls) elevations in liver biochemistries during a 6-month follow-up were categorized into mild-moderate or severe. Compared to statin controls, patients with elevated baseline liver enzymes had higher incidence of mild-moderate elevations (4.7% vs. 1.9%, P = .002) but not severe elevations (0.6% vs. 0.2%, P = 0.2). However, patients with elevated baseline liver enzymes who received statins did not have higher incidence of mild-moderate elevations (4.7% vs. 6.4%, P = .2) or severe elevations (0.6% vs. 0.4%, P = .6) than the liver disease controls who did not receive statins. These data showed that some individuals with elevated baseline liver enzymes have increases in their liver biochemistries, whether or not they receive statins (Singh et al., 2011). One may suggest that hyperlipidemic patients with elevated baseline liver enzymes in this study predominantly had NAFLD, as they had no evidence of other common etiologies (e.g. HBV or HCV or alcohol abuse) (Plaz Torres et al., 2020).

Concerning rosuvastatin group (20mg, and 40 mg doses) there was significant difference between the two doses with mean 3X elevation in ALT levels in 40 mg dose, suggesting significant effect of this dose on transaminase level. This in contrary to previously mentioned in the controlled clinical trials of rosuvastatin, the incidence of clinically significant ALT increases was low and similar across all doses: 0.5% at 5mg (among 1,317 patients), 0.1% at 10 mg (among 7,726 patients), 0.1% at 20 mg (among 3,882 patients), and 0.3% at 40 mg (among 3,957 patients) (Olsson et al., 2002).

5. CONCLUSION

Statin induce asymptomatic hepatitis, increases in the liver enzymes are related to the statin dose.

Author contribution

Thuraya Salim Abed: Conception and design of the work, the acquisition, analysis, and interpretation of data for the work, and Drafting the work.

Iyad Abbas Salman: Conception and design of the work, interpretation of data for the work, and revising it critically for important intellectual content

Mohammed Kassim A. Hassan: Conception and design of the work, and Drafting the work and finally revising it critically for important intellectual content

Funding

This study was funded by authors only.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed consent

Written informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval for human

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Code: 2019/A113).

Data and materials availability

All data associated with this study are present in the paper.

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